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(54) **Title:** CB1 ANTAGONIST AND A DYSLIPIDEMIC AGENT AND/OR METABOLIC REGULATOR, AND METHODS OF MAKING AND USING SAME

(57) **Abstract:** The present invention relates to a CB1 antagonist and a dyslipidemic agent and/or a metabolic regulator. The present invention further includes methods of using formulations of a CB1 antagonist and at least one of (a) omega-3 fatty acids, (b) MTP inhibitors, (c) DPP4 inhibitors, (d) sarsasapogenin, (e) smilagenin, (f) steroidal glycosides and/or (g) extracts of Artemisia spp. for treating various dyslipidemias; treating vascular disease; treating artherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; reducing the incidence of and/or delaying the onset of metabolic syndrome; and reducing the incidence of, and/or delay the onset of type II diabetes.

CB1 Antagonist and a Dyslipidemic Agent andlor Metabolic Regulator, and Methods of Making and Using Same

Background of the Invention

1. Field of the Invention

[0001] The present invention relates, generally, to compositions comprising a cannabinoid 1 (CB1) antagonist and a dyslipidemic agent and/or a metabolic regulator. Presently preferred dyslipidemic agents used in the compositions of the present invention may include, but are not limited to, omega-3 fatty acids, peroxisome proliferator-activated receptor (PPAR) agonists/antagonists, microsomal triglyceride transfer protein (MTP) inhibitors, and/or dipeptidyl peptidase-4 (DPP4) inhibitors. Presently preferred metabolic regulators used in the compositions of the present invention may include, but are not limited to, sarsasapogenin, smilagenin, steroidal glycosides and extracts thereof, and extracts of *Artemisia spp.* The present invention also includes pharmaceutical formulations made from the compositions, and methods of making such formulations. The present invention also includes methods of using formulations of a CB1 antagonist and at least one of (a) omega-3 fatty acids, (b) MTP inhibitors, (c) DPP4 inhibitors, (d) sarsasapogenin, (e) smilagenin, (f) steroidal glycosides and extracts thereof, and/or (g) extracts of *Artemisia spp.* for treating hypertriglyceridemia, hypercholesteremia, mixed dyslipidemia, vascular disease, artherosclerotic disease, and/or obesity; preventing and/or reducing cardiovascular and/or vascular events; reducing insulin resistance, fasting glucose levels, and/or postprandial glucose levels; and preventing and/or reducing the incidence of and/or delaying the onset of metabolic syndrome. The present invention further includes methods of using formulations of a CB1 antagonist and at least one of (a) omega-3 fatty acids, (b) MTP inhibitors, (c) DPP4 inhibitors, (d) PPAR agonists/antagonists, (e) sarsasapogenin, (f) smilagenin, (g) steroidal glycosides and extracts thereof, and/or (h) extracts of *Artemisia spp.* for preventing, reducing the incidence of, and/or delaying the onset of type II diabetes.

2. Description of the Related Art

[**0002**] Dyslipidemia is a general term used to describe various disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested in various ways, such as by elevation of total cholesterol, elevation of "bad" low-density lipoprotein cholesterol and/or triglyceride concentrations, and reduction in "good" high-density lipoprotein cholesterol concentrations. In humans, cholesterol and triglycerides are part of lipoprotein complexes in the bloodstream, and can be separated via ultracentrifugation into high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) fractions. Cholesterol and triglycerides are synthesized in the liver, incorporated into VLDL, and released into the plasma.

[**0003**] Dyslipidemia is often associated with diabetes and high blood pressure, particularly in obese/overweight patients. The relationship can also be observed in pre-diabetic patients who exhibit “metabolic syndrome” or "Syndrome X," which is characterized by the presence of metabolic risk factors that may include 1) central obesity; 2) atherogenic dyslipidemia (blood fat disorders comprising mainly high triglycerides (“TG”) and low HDL-cholesterol (interchangeably referred to herein as “HDL”) that foster plaque buildups in artery walls); 3) raised blood pressure; 4) insulin resistance or glucose intolerance (the body can’t properly use insulin or blood sugar); 5) prothrombotic state (*e.g.*, high fibrinogen or plasminogen activator inhibitor in the blood); and 6) a proinflammatory state (*e.g.*, elevated high-sensitivity C-reactive protein in the blood). The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines define metabolic syndrome by the presence of three of the following five clinical parameters: a) a waist circumference greater than 102 cm for men, and greater than 88 cm for women; b) a triglyceride level greater than 150 mg/dl; c) an HDL-cholesterol less than 40 mg/dl for men, and less than 50 mg/dl for women; d) a blood pressure greater than or equal to 130/85 mmHG; and e) a fasting glucose greater than 110 mg/dl (or fasting glucose greater than 125 mg/dl, if 3 or more of the other criteria are present). Patients exhibiting the symptoms of metabolic syndrome are at increased

risk of coronary heart disease and other diseases related to plaque buildups in artery walls (*e.g.*, stroke and peripheral vascular disease). It is estimated that over 50 million Americans have metabolic syndrome.

[0004] The epidemics of obesity, type II diabetes, hypertension, and metabolic syndrome continue to worsen. These patients frequently do not respond to single-agent therapy, and many require combinations of drugs to address the various metabolic problems causing changes in their lipoprotein fractions. Although the need for combination therapy has been established in the management of hypertension and type II diabetes, it is less often used for the treatment of dyslipidemia. Most of the medications currently available for treating dyslipidemia fail to address the various additional conditions that are often associated therewith. It would therefore be desirable to provide compositions and methods for treating dyslipidemia, particularly in patients also suffering from obesity, type II diabetes, hypertension, and/or metabolic syndrome. There is a need in the art for compositions and methods for improving lipid profiles in patients suffering from obesity, type II diabetes, hypertension, and/or metabolic disorder.

[0005] Omega-3 fatty acids are known to reduce serum triglycerides by inhibiting diacylglycerol acyltransferase (DGAT) and by stimulating peroxisomal and mitochondrial beta oxidation. Marine oils, also commonly referred to as fish oils, are a good source of two omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have been found to regulate lipid metabolism. Omega-3 fatty acids may include, but are not limited to, omega-3 polyunsaturated, long-chain fatty acids such as a eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and α-linolenic acid; esters of omega-3 fatty acids, optionally with glycerol, such as mono-, di- and triglycerides; and esters of the omega-3 fatty acids and a primary, secondary or tertiary alcohol such as fatty acid methyl esters and fatty acid ethyl esters. Omega-3 fatty acids or their esters, derivatives, conjugates, precursors, salts and mixtures thereof can be used either in their pure form or as a component of an oil such as fish oil, preferably

purified fish oil concentrates. Omega-3 fatty acids have been found to have beneficial effects on the risk factors for cardiovascular diseases, especially mild hypertension, hypertriglyceridemia and on the coagulation factor VII phospholipid complex activity. Omega-3 fatty acids lower serum triglycerides, increase serum HDL-cholesterol, lower systolic and diastolic blood pressure and the pulse rate, and lower the activity of the blood coagulation factor VII-phospholipid complex. Further, omega-3 fatty acids seem to be well-tolerated, without giving rise to any severe side effects.

[**0006**] One form of omega-3 fatty acid is a concentrate of omega-3, long chain, polyunsaturated fatty acids from fish oil containing DHA and EPA that is sold under the trademark LOVAZA™, which was formerly known as OMACOR®. Such a form of omega-3 fatty acid is described, for example, in U.S. Patent Nos. 5,502,077, 5,656,667 and 5,698,594, each of which is incorporated herein by reference.

[**0007**] Improving cholesterol and lipid levels is very important for long-term cardiovascular health, and is particularly important for reducing morbidity in patients who are also suffering from high blood pressure, type II diabetes, obesity, and/or metabolic syndrome. Various approaches have been taken to treat dyslipidemia.

[**0008**] U.S. Published Application No. 2005/0281868 describes a transdermal patch for combination therapy with a statin and another compound, for use in treating dyslipidemia. Exemplary transdermal products include any known statin that may be transdermally administered, in combination with various drugs, including rimonabant.

[**0009**] U.S. Published Application No. 2005/0171140 describes HMG CoA reductase inhibitors that may be useful for modulating blood serum lipids. These compounds may be combined with CB1 antagonists or inverse agonists, such as SR-141716 (Sanofi) and FLV-319 (Solvay).

[**0010**] U.S. Published Application No. 2005/0101542 describes a combination therapy for controlling appetite, including a combination of a PPAR-alpha agonist, such as oleoylethanolamide and oleoylethanolamide-like fatty acid alkanolamide compounds, and a CB1 cannabinoid receptor antagonist, such as SR-141716. Preferred PPAR-alpha agonists are clofibrate and derivatives of clofibrate such as fenofibrate, bezafibrate, gemfibrozil, and ciprofibrate. The combination was described as synergistically reducing appetite and promoting weight loss when administered to a patient. The combination therapy may be used to prevent or treat diseases associated with obesity or overweight in mammals, and may also be useful for modulating lipid metabolism.

[**0011**] U.S. Patent No. 6,875,782 describes substituted heterocyclic derivatives which modulate blood glucose levels, triglyceride levels, insulin levels, and non-esterified fatty acid levels. The compounds may be combined with various dyslipidemic agents, including fibrates, PPAR agonists, MTP inhibitors, CAIs, statins, CETP, niacin derivatives, LXR, etc. (col. 37, line 6 – col. 41, line 8). The compounds may also be combined with anorectic agents, including cannabinoid receptor antagonists, such as SR-141716/rimonabant (Sanofi) or SLV-318 (Solvay).

[**0012**] U.S. Published Application Nos. 2005/0192278, 2005/0171110, and 2005/0143381 are related, and discuss azabicyclic heterocycles as cannabinoid receptor modulators, preferably antagonists or inverse agonists of CB1. These compounds may be combined with hypolipidemic agents, such as HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, bile acid sequestrants, nicotinic acid (niacin), acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives, quaternary amine poly(diallyldimethylammonium chloride) and ionenes, and other serum cholesterol lowering agents. The hypolipidemic agent may also be an ACAT inhibitor, an upregulator of LDL receptor activity, a cholesterol absorption inhibitor, a cholesteryl transfer protein inhibitor (CETP), an ileal Na+/bile acid co-transporter inhibitor, or an ATP citrate lyase inhibitor. Other lipid

agents for possible use with the compounds include phytoestrogen compounds, beta-lactam cholesterol absorption inhibitors, HDL upregulator such as LXR agonists, PPAR alpha-agonists and/or FXR agonists, LDL catabolism promoters, sodium-proton exchange inhibitors, LDL-receptor inducers, steroidal glycosides, anti-oxidants, isoniazid, HMG-CoA synthase inhibitors, lanosterol demethylase inhibitors, PPAR delta agonists, sterol regulating element binding protein-I (SREBP-1), and sphingolipids. The compounds may also be combined with anti-diabetic agents, such as PPAR gamma agonists and PPAR alpha/gamma dual agonists.

[**0013**] U.S. Published Application No. 2005/0182103 describes substituted diphenyl pyridines that are antagonists and/or inverse agonists of CB1. These compounds may be combined with antipsychotic agents, cognition-enhancing agents, anti-migraine agents, anti-asthmatic agents, anti-inflammatory agents, anxiolytics, anti-Parkinson's agents, anti-epileptic agents, anorectic agents, serotonin reuptake inhibitors, and other anti-obesity agents. Use of the compounds to treat co-morbidities of obesity, such as dyslipidemia, is discussed.

[**0014**] U.S. Published Application Nos. 2004/0214856, 2004/0214855, 2004/0214838, 2004/0214837, and 2004/0157839 are related, and describe various compounds believed to be cannabinoid receptor ligands, more particularly CB1 antagonists. Other suitable pharmaceutical agents may be administered in combination with anti-obesity agents, anti-hypertensive agents, cannabinoid receptor ligands, including lipid-lowering agents, cholesterol biosynthesis inhibitors, and cholesterol absorption inhibitors. These other agents may include glitazones, HMG-CoA reductase inhibitors, HMG-CoA synthase inhibitors, HMG-CoA reductase or synthase gene expression inhibitors, CETP inhibitors, bile acid sequestrants, fibrates, ACAT inhibitors, squalene synthetase inhibitors, anti-oxidants, and nicotinic acid (niacin). Naturally occurring compounds (commonly called nutraceuticals) that act to lower plasma cholesterol levels may also be included, such as garlic extract, Hoodia plant extracts, and niacin.

[**0015**] U.S. Published Application No. 2002/0055539 relates to compositions and methods for treating or preventing cardiovascular conditions by intravascular administration of an omega fatty acid. The cardiovascular condition may be peripheral vascular disease. The compositions may include one or more omega-3 fatty acids, one or more omega-6 fatty acids, or a mixture of one or more omega-3 and one or more omega-6 fatty acids. In accordance with the methods of treatment, the composition is preferably administered intravascularly in close proximity to the site to be treated.

[**0016**] There is clearly a great need in the art for compositions that are useful for treating dyslipidemia, particularly dyslipidemia that is present in obese patients, and patients with type II diabetes, high blood pressure, and/or metabolic syndrome. Methods of treating dyslipidemia using the formulations are also needed, particularly in patients with obesity, type II diabetes, high blood pressure, and/or metabolic syndrome.

Summary of the Invention

[**0017**] The present invention provides compositions comprising a CB1 antagonist and a dyslipidemic agent and/or metabolic regulator. Compositions of the invention are useful for treating various dyslipidemias, including hypertriglyceridemia, hypercholesteremia, and mixed dyslipidemia; vascular disease; artherosclerotic disease; and related conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic disease. These compositions of the invention may also be useful for treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome.

[**0018**] The present invention also provides methods of treating various dyslipidemias, including hypertriglyceridemia, hypercholesteremia, and mixed dyslipidemia; treating vascular disease; treating artherosclerotic disease; treating or preventing conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic

disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome. These diseases and conditions may be treated and/or prevented by administering a composition including a CB1 antagonist in combination with a dyslipidemic agent and/or a metabolic regulator. The CB1 antagonist and dyslipidemic agent and/or metabolic regulator may be administered in the same composition, or concomitantly in separate compositions, as described herein.

[0019] One embodiment of the present invention includes a combination product including one or more dyslipidemic agents selected from DPP4 inhibitors, MTP inhibitors, and omega-3 fatty acids, and one or more compounds that act as antagonists of CB1 receptors. Such a combination product may be provided, for example, in a unit dosage form. In some embodiments, such compositions are useful for treating various dyslipidemias, including hypertriglyceridemia, hypercholesteremia, and mixed dyslipidemia; treating vascular disease; treating artherosclerotic disease; treating or preventing conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome, wherein one or more dyslipidemic agents are combined with the CB1 antagonist to provide specific therapeutic properties. According to some embodiments, the combination product further comprises one or more metabolic regulators.

[0020] Another embodiment of the present invention includes a combination product including one or more PPAR agonists/antagonists and one or more compounds that act as an antagonist of CB1 receptors. Such a combination product may be provided, for example, in a unit dosage form. In some embodiments, such compositions are useful

for treating various dyslipidemias, including hypertriglyceridemia, hypercholesteremia, and mixed dyslipidemia; treating vascular disease; treating artherosclerotic disease; treating or preventing conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome, wherein one or more PPAR agonists/antagonists are combined with one or more CB1 antagonists to provide specific therapeutic properties. According to some embodiments, the combination product further comprises one or more metabolic regulators.

[0021] Another embodiment of the present invention includes a combination product including one or more metabolic regulators selected from sarsasapogenin, smilagenin, steroidal glycosides and extracts thereof, and extracts of *Artemisia spp.*, and one or more compounds that act as an antagonist of CB1 receptors. Such a combination product may be provided, for example, in a unit dosage form. In some embodiments, such compositions are useful for treating various dyslipidemias, including hypertriglyceridemia, hypercholesteremia, and mixed dyslipidemia; treating vascular disease; treating artherosclerotic disease; treating or preventing conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome, wherein one or more metabolic regulators are combined with the CB1 antagonist to provide specific therapeutic properties. According to some embodiments, one or more dyslipidemic agents and/or PPAR agonists/antagonists may also be provided.

[**0022**] Another embodiment of the present invention includes methods of treating patients by administering compositions containing one or more dyslipidemic agents selected from omega-3 fatty acids, MTP inhibitors, and DPP4 inhibitors, and one or more compounds that act as antagonists of CB1 receptors. These methods provide an effective treatment for patients suffering from hypertriglyceridemia, hypercholesteremia, mixed dyslipidemia, vascular disease, artherosclerotic disease and/or related conditions. The methods also may be beneficially used to treat obesity, to prevent or reduce cardiovascular and vascular events, reduce insulin resistance, fasting glucose levels and postprandial glucose levels, treating and/or preventing diabetes and/or symptoms thereof, and/or to prevent and/or reduce the incidence of and/or the delay of onset of type II diabetes and/or metabolic syndrome. According to a preferred embodiment, the one or more dyslipidemic agents and one or more CB1 antagonists are provided for co-administration, or as unit doses, with one or more additional compounds that are also useful for treating dyslipidemia and any of the various conditions associated therewith. According to some embodiments, one or more metabolic regulators may also be administered.

[**0023**] Another embodiment of the present invention includes methods of treating patients by administering compositions containing one or more metabolic regulators selected from sarsasapogenin, smilagenin, steroidal glycosides and extracts thereof, and extracts of *Artemisia spp.*, and one or more compounds that act as antagonists of CB1 receptors. These methods provide an effective treatment for patients suffering from hypertriglyceridemia, hypercholesteremia, mixed dyslipidemia, vascular disease, artherosclerotic disease and/or related conditions. The methods also may be beneficially used to treat obesity, to prevent or reduce cardiovascular and vascular events, reduce insulin resistance, fasting glucose levels and postprandial glucose levels, to treat and/or prevent diabetes and/or symptoms thereof, and/or to prevent and/or reduce the incidence of and/or the delay of onset of type II diabetes and/or metabolic syndrome. According to a preferred embodiment, the one or more metabolic regulators and one or more CB1 antagonists are provided for co-administration, or as

unit doses, with one or more additional compounds that are also useful for treating dyslipidemia and any of the various conditions associated therewith. According to some embodiments, one or more dyslipidemic agents and/or PPAR agonists/antagonists may also be administered.

[**0024**] A further embodiment of the present invention includes methods of treating patients by administering one or more PPAR agonists/ antagonists and one or more compounds that act as antagonists of CB1 receptors. These methods may be useful for treating patients suffering from various dyslipidemias, including hypertriglyceridemia, hypercholesteremia, and mixed dyslipidemia; treating vascular disease; treating artherosclerotic disease; treating or preventing conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome. According to a preferred embodiment, the one or more PPAR agonists/antagonists and one or more CB1 antagonists are provided for co-administration, or as unit doses, with one or more additional compounds that are also useful for treating patients suffering from various dyslipidemias, including hypertriglyceridemia, hypercholesteremia, and mixed dyslipidemia; treating vascular disease; treating artherosclerotic disease; treating or preventing conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome. According to some embodiments, one or more metabolic regulators may also be administered.

[0025] The present invention also provides a composition comprising omega-3 fatty acids in combination with one or more compounds that antagonize the CB1 receptor, in order to provide an effective pharmaceutical treatment for dyslipidemia, which in some embodiments minimizes unwanted side effects and provides relief from other conditions commonly-associated with dyslipidemia, such as, but not limited to, obesity and type II diabetes. According to another embodiment, the composition including omega-3 fatty acids and a CB1 receptor antagonist also includes another compound useful in treating various dyslipidemias, including hypertriglyceridemia, hypercholesteremia, and mixed dyslipidemia; treating vascular disease; treating artherosclerotic disease; treating or preventing conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome.

[0026] One embodiment of the present invention provides a method of making a composition comprising one or more compounds that act as antagonists of CB1 receptors, and one or more dyslipidemic agents and/or one or more metabolic regulators, for the treatment of subjects with dyslipidemia. Preferably, the dyslipidemic agents may be selected from omega-3 fatty acids, PPAR agonists/antagonists, MTP inhibitors, and DPP4 inhibitors. According to a presently preferred embodiment, the dyslipidemic agent comprises omega-3 fatty acids. Preferably, the metabolic regulators may be selected from sarsasapogenin, smilagenin, steroidal glycosides, and extracts of *Artemisia spp*.

[0027] Another embodiment of the present invention is an oral formulation of one or more compounds that act as antagonists of CB1 receptors, and one or more dyslipidemic agents and/or one or more metabolic regulators. Preferably, the dyslipidemic agents may be selected from omega-3 fatty acids, PPAR

agonists/antagonists, MTP inhibitors, and DPP4 inhibitors. According to a presently preferred embodiment, the dyslipidemic agent comprises omega-3 fatty acids. Preferably, the metabolic regulators may be selected from sarsasapogenin, smilagenin, steroidal glycosides, and extracts of *Artemisia spp*.

[**0028**] Another subject of the invention is a method of relieving dyslipidemia in a patient suffering therefrom, by providing a composition comprising one or more compounds that act as antagonists of CB1 receptors, and one or more dyslipidemic agents and/or one or more metabolic regulators, and thereafter administering the composition to the patient. Preferably, the dyslipidemic agents may be selected from omega-3 fatty acids, PPAR agonists/antagonists, MTP inhibitors, and DPP4 inhibitors. According to a presently preferred embodiment, the dyslipidemic agent comprises omega-3 fatty acids. Preferably, the metabolic regulators may be selected from sarsasapogenin, smilagenin, steroidal glycosides, and extracts of *Artemisia spp*.

[**0029**] Another subject of the invention is the use of one or more compounds that act as antagonists of CB1 receptors, and one or more dyslipidemic agents and/or one or more metabolic regulators, for the manufacture of a medicament for treating dyslipidemia. Preferably, the dyslipidemic agents may be selected from omega-3 fatty acids, PPAR agonists/antagonists, MTP inhibitors, and DPP4 inhibitors. According to a presently preferred embodiment, the dyslipidemic agent comprises omega-3 fatty acids. Preferably, the metabolic regulators may be selected from sarsasapogenin, smilagenin, steroidal glycosides, and extracts of *Artemisia spp*.

[**0030**] The compositions and methods of the present invention may further comprise co-administration of one or more additional compounds useful in the treatment of one or more of obesity, type II diabetes, hypertension, and/or metabolic syndrome. According to a particularly preferred embodiment, the compositions and methods of the present invention are useful in the treatment of obesity. Also included are unit dosage forms including the dyslipidemic agents and/or metabolic regulators, and CB1 antagonists,

along with one or more of said additional compounds, and methods for administering same to a patient in need thereof.

[0031] The additional compounds may be selected from the group consisting of carbonic anhydrase inhibitors (CAIs), statins, cholesteryl ester transfer protein (CETP) inhibitors, niacin derivatives, and liver X receptor (LXR) agonists/antagonists. The additional compounds may further be selected from anti-obesity agents, such as melanocortin receptor (MC4R) agonists, melanin-concentrating hormone receptor (MCHR) antagonists, growth hormone secretagogue receptor (GHSR) antagonists, orexin receptor antagonists, cholecystokinin (CCK) agonists, glucagon-like peptide-1 (GLP-1) agonists, neuropeptide Y1 or Y5 (NPY1 or NPY5) antagonists, corticotropin releasing factor (CRF) antagonists, histamine receptor-3 (H3) modulators, beta-3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, serotonin receptor agonists, activating protein 2 (aP2) inhibitors, thyroid receptor agonists and anorectic agents; anti-diabetic agents, such as antihyperglycemic agents including insulin secretagogues or insulin sensitizers, biguanides, sulfonyl ureas, glucosidase inhibitors, sodium-glucose co-transporter type 2 (SGLT2) inhibitors, glycogen phosphorylase inhibitors, protein tyrosine phosphatase-1B (PTP-1B) inhibitors, 11β-hydroxy-steroid dehydrogenase 1 (11β-HSD 1) inhibitors and/or meglitinides, as well as insulin; and anti-hypertensive agents, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, neutral endopepsidase/angiotensin-converting enzyme (NEP/ACE) inhibitors, as well as calcium channel blockers, β-adrenergic blockers, and diuretics.

[0032] Other novel features and advantages of the present invention will become apparent to those skilled in the art upon examination of the following or upon learning by practice of the invention.

Detailed Description of the Invention

[0033] The present invention relates to compositions comprising a CB1 antagonist, and a dyslipidemic agent and/or a metabolic regulator, methods of making same, their use in treating various dyslipidemias, including hypertriglyceridemia, hypercholesteremia, and mixed dyslipidemia; treating vascular disease; treating artherosclerotic disease; treating or preventing conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome. Additional compounds useful in treating these and related conditions may also be beneficially coadministered with the inventive compositions and pharmaceutical formulations, or may be provided in a unit dose form therewith. According to one presently preferred embodiment, the compositions and methods of the present invention include omega-3 fatty acids, preferably the LOVAZA™ omega-3 fatty acids.

[0034] In preferred embodiments the pharmaceutical compositions include omega-3 fatty acids as described in U.S. Patent Nos. 5,502,077, 5,656,667 and 5,698,594, including, but not limited to, the omega-3 fatty acids marketed as LOVAZA™. In other preferred embodiments the pharmaceutical compositions comprise omega-3 fatty acids present in a concentration of at least 40% by weight as compared to the total fatty acid content of the composition. In still other preferred embodiments the omega-3 fatty acids comprise at least 50% by weight of EPA and DHA as compared to the total fatty acid content of the composition, and the EPA and DHA are in a weight ratio of EPA:DHA of from 99:1 to 1:99, preferably from 1:4 to 4:1, more preferably from 1:3 to 3:1, and most preferably from 1:2 to 2:1. The omega-3 fatty acids may comprise pure EPA or pure DHA.

1. Compositions Comprising a Dyslipidemic Agent and/or a Metabolic Regulator and a CB1 Antagonist

[**0035**] The compositions of the present invention include one or more dyslipidemic agents and/or one or more metabolic regulators, and one or more CB1 antagonists. The compositions may optionally include one or more additional compounds useful in treating various dyslipidemias, including hypertriglyceridemia, hypercholesteremia, and mixed dyslipidemia; treating vascular disease; treating artherosclerotic disease; treating or preventing conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome. The compositions may be provided as pharmaceutical formulations for use in treating these and other health conditions involving a dyslipidemia component.

[**0036**] The compositions of the present invention encompass combination products in which the dyslipidemic agent(s) and/or metabolic regulator(s), and one or more CB1 antagonists are administered separately as part of a concomitant dosing regimen. The compositions of the present invention also encompass unit dosage forms in which the dyslipidemic agent(s) and/or metabolic regulator(s) are incorporated together with the one or more CB1 antagonists into a single dose. Regardless of whether the compositions are provided as combination products or unit dosage forms, each dose preferably includes from 10 to 95% dyslipidemic agent(s) and/or metabolic regulator(s) by weight of the composition, and from 10 to 95% CB1 antagonist(s) by weight of the composition. According to one embodiment, the compositions include from 30 to 99.9% omega-3 fatty acids, and from 0.1 to 70% of one or more CB1 antagonists, by weight of the composition. According to a further embodiment, the compositions containing omega-3 fatty acids and one or more CB1 antagonists may also include from 0.1 to

70% of one or more additional dyslipidemic agents and/or metabolic regulators, by weight of the composition.

A. Dyslipidemic Agents

[**0037**] The dyslipidemic agents that may be used in accordance with the present invention may be selected from any compounds useful in regulating the balance of lipids in the blood, regardless of whether those compounds are considered to be pharmaceuticals, nutraceuticals, or homeopathic/naturopathic agents. Presently preferred dyslipidemic agents include PPAR agonists/antagonists, DPP4 inhibitors, MTP inhibitors, and omega-3 fatty acids, although the use of other dyslipidemic agents is also envisioned. The presently preferred dyslipidemic agents are further described below.

i. Omega-3 Fatty Acids

[**0038**] As used herein, the term "omega-3 fatty acids" includes natural or synthetic omega-3 fatty acids, or pharmaceutically acceptable esters, derivatives, conjugates (see, e.g., Zaloga et al., U.S. Patent Application Publication No. 2004/0254357, and Horrobin et al., U.S. Patent No. 6,245,811, each hereby incorporated by reference), precursors or salts thereof and mixtures thereof. Examples of omega-3 fatty acid oils include but are not limited to omega-3 polyunsaturated, long-chain fatty acids, where the omega-3 polyunsaturated long-chain fatty acids preferably include chains of 14-22 carbon atoms, more preferably include chains of 16-22 carbon atoms, and most preferably include chains of 18-22 carbon atoms, and where particularly preferred omega-3 polyunsaturated long-chain fatty acids are eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), α-linolenic acid, stearidonic acid, eicosatetraenoic acid, and docosapentaenoic acid; esters of omega-3 fatty acids with glycerol such as mono-, di- and triglycerides; and esters of the omega-3 fatty acids and a primary, secondary or tertiary alcohol such as fatty acid methyl esters and fatty acid ethyl esters. Preferred omega-3 fatty acid oils are long-chain fatty acids such as EPA or DHA, triglycerides thereof, ethyl esters thereof and mixtures thereof. The omega-3 fatty acids or their

esters, derivatives, conjugates, precursors, salts and mixtures thereof can be used either in their pure form or as a component of an oil such as fish oil, preferably purified fish oil concentrates. Commercial examples of omega-3 fatty acids suitable for use in the invention include Incromega F2250, F2628, E2251, F2573, TG2162, TG2779, TG2928, TG3525 and E5015 (Croda International PLC, Yorkshire, England), and EPAX6000FA, EPAX5000TG, EPAX4510TG, EPAX2050TG, EPAX6015TG/EE, EPAX4510TG, EPAX4020TG/EE, EPAX6000TG/EE, EPAX5500EE, EPAX1050TG, K85TG, K85EE, K80EE and EPAX7010EE (EPAX AS, NO-6028 Aalesund, Norway).

[0039] Another preferred composition includes omega-3 fatty acids present in a concentration of at least 40% by weight, preferably at least 50% by weight, more preferably at least 60% by weight, still more preferably at least 70% by weight, most preferably at least 80% by weight, or even at least 90% by weight. Preferably, the omega-3 fatty acids comprise at least 50% by weight of EPA and DHA, more preferably at least 60% by weight, still more preferably at least 70% by weight, most preferably at least 80%, such as about 84% by weight. Preferably the omega-3 fatty acids comprise about 5 to about 100% by weight, more preferably about 25 to about 75% by weight, still more preferably about 40 to about 55% by weight, and most preferably about 46% by weight of EPA. Preferably the omega-3 fatty acids comprise about 5 to about 100% by weight, more preferably about 25 to about 75% by weight, still more preferably about 30 to about 60% by weight, and most preferably about 38% by weight of DHA. All percentages above are by weight as compared to the total fatty acid content in the composition, unless otherwise indicated. The percentage by weight may be based on the free acid or ester forms, although it is preferably based on the ethyl ester form of the omega-3 fatty acids even if other forms are utilized in accordance with the present invention.

[0040] The omega-3 fatty acids can be present in the compositions for co-administration, or in the unit dosage forms, in an amount from about 350 mg to about 10 grams, more preferably about 500 mg to about 6 grams, and most preferably from about

750 mg to about 4 grams. According to one embodiment, about 1 gram of omega-3 fatty acids is provided. According to another embodiment, this amount of omega-3 fatty acids is administered daily, although it is also envisioned that the compositions for co-administration and unit dosage forms may be administered under varying dosing regimens. The total dose of omega-3 fatty acids may be administered in one or more dosage units, preferably one dosage unit. The omega-3 fatty acid composition optionally includes chemical antioxidants, such as alpha tocopherol, oils, such as soybean oil and partially hydrogenated vegetable oil, and lubricants such as fractionated coconut oil, lecithin and a mixture of the same.

[**0041**] The most preferred form of omega-3 fatty acids is LOVAZA™ omega-3 fatty acids (K85EE, Pronova Biocare A.S., Lysaker, Norway), which preferably have the following characteristics (per dosage form):

Test	**Minimum Value**	**Maximum Value**
Eicosapentaenoic acid C20:5	430 mg/g	495 mg/g
Docosahexaenoic acid C22:6	347 mg/g	403 mg/g
EPA and DHA	800 mg/g	880 mg/g
Total n-3 fatty acids	90 % (w/w)	

[**0042**] The daily dosages of CB1 antagonist and omega-3 fatty acids can be administered together in from 1 to 10 dosages, with the preferred number of dosages from 1 to 4 times a day, most preferred 1 to 2 times a day. The administration is preferably oral administration, although other forms of administration that provides a unit dosage of CB1 antagonist and omega-3 fatty acids may be used.

[**0043**] When used in accordance with the methods of the present invention, the omega-3 fatty acids may be administered in an amount more than, equal to or less than the conventional full-strength dose as a single-administered product. For example, the omega-3 fatty acids may be administered in an amount of from 10-100%, preferably about 25-100%, most preferably about 50-80%, of the conventional full-strength dose as a single-administered product.

ii. PPAR Agonists/Antagonists

[**0044**] According to a further preferred embodiment, the inventive compositions may comprise a peroxisome proliferator activating receptor (PPAR) agonist and/or antagonist as a dyslipidemic agent. There are 3 known subtypes of PPARs: PPAR-alpha (which includes the fibrates, as discussed above), PPAR-delta, and PPAR-gamma. The PPARs are members of the nuclear hormone receptor subfamily of transcription factors. The gene for PPAR-gamma is located in chromosome band 3p25, and is responsible for regulating the development of adipocytes (fat cells). This transcription factor is expressed early in the differentiation of preadipocytes, and is also important in the proper maintenance of function in the mature adipocyte, for example, in the ongoing expression of genes encoding lipid oxidative enzymes.

[**0045**] The present invention may incorporate now known or future known PPAR agonists and/or antagonists in an amount generally recognized as safe. The term "PPAR agonists and/or antagonists" includes, but is not limited to, PPAR-alpha modulators, PPAR-gamma modulators, and PPAR-delta modulators, as well as dual-PPAR modulators such as PPAR-alpha/gamma modulators, PPAR-gamma/delta modulators, and PPAR-alpha/delta modulators. The PPAR agonists and/or antagonists may also include PPAR-alpha/gamma/delta agonists and antagonists. The PPAR agonists and/or antagonists may further include partial PPAR agonists and/or antagonists. Preferred PPAR agonists/antagonists may include, but are not limited to, fibrates, thiazolidinediones and non-thiazolidinediones; specifically preferred compounds include fenofibrate, bezafibrate, clofibrate, gemfibrozil, ciglitazone, metaglidasen, tesaglitazar, naviglitazar, mivaglitazar, muraglitazar, proglitazone, rosiglitazone, pioglitazone, and troglitazone.

[**0046**] Generally, the effect of the PPAR agonist and/or antagonist is dose dependent, *i.e.*, the higher the dose, the greater the therapeutic affect. However, the effect of each PPAR agonist and/or antagonist is different, and therefore the level of therapeutic effect

of PPAR agonist and/or antagonist cannot be necessarily be directly correlated to the level of therapeutic effects of other PPAR agonists and/or antagonists. However, those of ordinary skill in the art would understand the correct dosage to be given to a particular subject, based on experience and the seriousness of the condition.

[**0047**] The daily dosages of PPAR agonist and/or antagonist and CB1 antagonist can be administered together in from 1 to 10 dosages, with the preferred number of dosages from 1 to 4 times a day, most preferably 1 to 2 times a day. The administration is preferably oral administration, although other forms of administration that provides a unit dosage of PPAR agonist and/or antagonist and CB1 antagonist may be used.

[**0048**] When used in accordance with the methods of the present invention, the PPAR agonist and/or antagonist may be administered in an amount more than, equal to or less than the conventional full-strength dose as a single-administered product. For example, the PPAR agonist and/or antagonist may be administered in an amount of from 10-100%, preferably about 25-100%, most preferably about 50-80%, of the conventional full-strength dose as a single-administered product.

iii. MTP Inhibitors

[**0049**] According to a further preferred embodiment, the inventive compositions may comprise a microsomal triacylglycerol transfer protein (MTP) inhibitor as a dyslipidemic agent. Human microsomal triacylglycerol transfer protein (hMTP) is essential for apolipoprotein B (apoB)-lipoprotein assembly and secretion, and is known to transfer triacylglycerols, cholesterol esters, and phospholipids. MTP antagonists/blockers/ inhibitors that may be used in accordance with the present invention include implitapide, and the compounds presently known as JTT-130, CP-346086, BMS-200150, and BMS-201038.

[**0050**] The present invention may incorporate now known or future known MTP inhibitors in an amount generally recognized as safe. Generally, the effect of the MTP

inhibitor is dose dependent, *i.e.*, the higher the dose, the greater the therapeutic affect. However, the effect of each MTP inhibitor is different, and therefore the level of therapeutic effect of a MTP inhibitor cannot be necessarily be directly correlated to the level of therapeutic effects of other MTP inhibitor. However, those of ordinary skill in the art would understand the correct dosage to be given to a particular subject, based on experience and the seriousness of the condition.

[**0051**] The daily dosages of MTP inhibitor and CB1 antagonist can be administered together in from 1 to 10 dosages, with the preferred number of dosages from 1 to 4 times a day, most preferably 1 to 2 times a day. The administration is preferably oral administration, although other forms of administration that provides a unit dosage of MTP inhibitor and CB1 antagonist may be used.

[**0052**] When used in accordance with the methods of the present invention, the MTP inhibitor may be administered in an amount more than, equal to or less than the conventional full-strength dose as a single-administered product. For example, the MTP inhibitor may be administered in an amount of from 10-100%, preferably about 25-100%, most preferably about 50-80%, of the conventional full-strength dose as a single-administered product.

iv. <u>DPP4 Inhibitors</u>

[**0053**] According to a further preferred embodiment, the inventive compositions may comprise a dipeptidyl peptidase 4 (DPP4) inhibitor as a dyslipidemic agent. DPP4 is believed to degrade GLP-1 (glucagon-like peptide-1), a hormone that is released in response to the intake of food that stimulates pancreatic beta cells to increase the secretion of insulin. DPP4 inhibitors may block GLP-1 degradation, thereby maintaining a higher concentration of GLP-1 for a longer period of time. DPP4 inhibitors that are envisioned for use in accordance with the present invention include sitagliptin (Merck), SYR-322 (under development by Takeda), PHX1149 (under development by Phenomix), and vildagliptin (under development by Novartis).

[**0054**] The present invention may incorporate now known or future known DPP4 inhibitors in an amount generally recognized as safe. Generally, the effect of the DPP4 inhibitors is dose dependent, *i.e.*, the higher the dose, the greater the therapeutic affect. However, the effect of each DPP4 inhibitor is different, and therefore the level of therapeutic effect of a DPP4 inhibitor cannot be necessarily be directly correlated to the level of therapeutic effects of other DPP4 inhibitors. However, those of ordinary skill in the art would understand the correct dosage to be given to a particular subject, based on experience and the seriousness of the condition.

[**0055**] The daily dosages of a DPP4 inhibitor and CB1 antagonist can be administered together in from 1 to 10 dosages, with the preferred number of dosages from 1 to 4 times a day, most preferably 1 to 2 times a day. The administration is preferably oral administration, although other forms of administration that provides a unit dosage of a DPP4 inhibitor and CB1 antagonist may be used.

[**0056**] When used in accordance with the methods of the present invention, the DPP4 inhibitor may be administered in an amount more than, equal to or less than the conventional full-strength dose as a single-administered product. For example, the DPP4 inhibitor may be administered in an amount of from 10-100%, preferably about 25-100%, most preferably about 50-80%, of the conventional full-strength dose as a single-administered product.

B. Metabolic Regulators

[**0057**] The metabolic regulators that may be used in accordance with the present invention may be selected from any compounds useful in regulating metabolism, and preferably are useful in regulating, preventing, and/or treating metabolic imbalances, such as obesity and diabetes, regardless of whether those compounds are considered to be pharmaceuticals, nutraceuticals, or homeopathic/naturopathic agents. The preferred metabolic regulators are derived and/or extracted from natural sources,

particularly plants, and are most preferably derived and/or extracted from plants of the *Trichocaulon* family (i.e., *Hoodia spp.*, especially *Hoodia gordonii*, and *Larryleachia spp.*), *Artemisia spp.* (i.e., *Artemesia herba-alba*, *Artemesia afra*, *Artemisia dracunculus*, *Artemisia vulgaris*), and/or plants of the *Sarsaparilla* family (i.e., *Smilax officinalis*, *Smilax aristolochiaefolia*, *Smilax glabra*, *Smilax febrifuga*, *Smilax ornata*, *Smilax regelii*, *Smilax japicanga*). The compounds derived and/or extracted from plants may be provided in any form suitable for use in conjunction with the compositions and methods of the present invention. Presently preferred metabolic regulators include sarsasapogenin, smilagenin, steroidal glycosides, and extracts of *Artemisia spp.*, although the use of other metabolic regulators is also envisioned. The presently preferred metabolic regulators are further described below.

i. Sarsasapogenin

[**0058**] According to a further preferred embodiment, the inventive compositions may comprise sarsasapogenin. Sarsasapogenin is believed to be useful in treating obesity, diabetes, and cognitive and neurodegenerative disorders. Sarsasapogenin for use in accordance with the present invention may be prepared in accordance with the methods set forth in published application WO 06/48665.

[**0059**] The present invention may incorporate sarsasapogenin in an amount generally recognized as safe. Generally, the effect of the sarsasapogenin is dose dependent, *i.e.*, the higher the dose, the greater the therapeutic affect. However, those of ordinary skill in the art would understand the correct dosage to be given to a particular subject, based on experience and the seriousness of the condition.

[**0060**] The daily dosages of sarsasapogenin and CB1 antagonist can be administered together in from 1 to 10 dosages, with the preferred number of dosages from 1 to 4 times a day, most preferably 1 to 2 times a day. The administration is preferably oral administration, although other forms of administration that provides a unit dosage of a sarsasapogenin and CB1 antagonist may be used.

[**0061**] When used in accordance with the methods of the present invention, the sarsasapogenin may be administered in an amount more than, equal to or less than the conventional full-strength dose as a single-administered product. For example, the sarsasapogenin may be administered in an amount of from 10-100%, preferably about 25-100%, most preferably about 50-80%, of the conventional full-strength dose as a single-administered product.

ii. Smilagenin

[**0062**] According to a further preferred embodiment, the inventive compositions may comprise smilagenin. Smilagenin is believed to be useful in treating hypercholesterolemia, obesity, diabetes, cognitive dysfunction, and non-cognitive neurodegeneration and neuromuscular impairment. Smilagenin for use in the present invention may be prepared in accordance with the methods set forth in published application WO 05/105825.

[**0063**] The present invention may incorporate smilagenin in an amount generally recognized as safe. Generally, the effect of the smilagenin is dose dependent, *i.e.*, the higher the dose, the greater the therapeutic affect. However, those of ordinary skill in the art would understand the correct dosage to be given to a particular subject, based on experience and the seriousness of the condition.

[**0064**] The daily dosages of smilagenin and CB1 antagonist can be administered together in from 1 to 10 dosages, with the preferred number of dosages from 1 to 4 times a day, most preferably 1 to 2 times a day. The administration is preferably oral administration, although other forms of administration that provides a unit dosage of a smilagenin and CB1 antagonist may be used.

[**0065**] When used in accordance with the methods of the present invention, the smilagenin may be administered in an amount more than, equal to or less than the

conventional full-strength dose as a single-administered product. For example, the smilagenin may be administered in an amount of from 10-100%, preferably about 25-100%, most preferably about 50-80%, of the conventional full-strength dose as a single-administered product.

iii. Steroidal Glycosides

[**0066**] According to a further preferred embodiment, the inventive compositions may comprise steroidal glycosides, particularly those extracted from plants of the genus *Trichocaulon* or *Hoodia*. Steroidal glycosides are believed to be useful in treating diabetes, and particularly non-insulin dependent diabetes, and as an appetite suppressant. Steroidal glycosides for use with the present invention may be prepared in accordance with the methods set forth in published application GB 2363985.

[**0067**] The present invention may incorporate steroidal glycosides in an amount generally recognized as safe. Generally, the effect of the steroidal glycosides is dose dependent, *i.e.*, the higher the dose, the greater the therapeutic affect. However, those of ordinary skill in the art would understand the correct dosage to be given to a particular subject, based on experience and the seriousness of the condition.

[**0068**] The daily dosages of steroidal glycosides and CB1 antagonist can be administered together in from 1 to 10 dosages, with the preferred number of dosages from 1 to 4 times a day, most preferably 1 to 2 times a day. The administration is preferably oral administration, although other forms of administration that provides a unit dosage of a steroidal glycosides and CB1 antagonist may be used.

[**0069**] When used in accordance with the methods of the present invention, the steroidal glycosides may be administered in an amount more than, equal to or less than the conventional full-strength dose as a single-administered product. For example, the steroidal glycosides may be administered in an amount of from 10-100%, preferably

about 25-100%, most preferably about 50-80%, of the conventional full-strength dose as a single-administered product.

iv. Extracts of *Artemisia spp.*

[**0070**] According to a further preferred embodiment, the inventive compositions may comprise extracts of *Artemisia spp*. Extracts of *Artemisia spp*. are believed to be effective against defective carbohydrate metabolism, to be insulinomimetic, and have glucagon antagonistic properties. Extracts of *Artemisia spp*. may be useful in treating type 2 diabetes and hyperglycemia. Extracts of *Artemisia spp*. for use with the present invention may be prepared in accordance with the methods set forth in published application WO 97/35598.

[**0071**] The present invention may incorporate extracts of *Artemisia spp*. in an amount generally recognized as safe. Generally, the effect of the extracts of *Artemisia spp*. are dose dependent, *i.e.*, the higher the dose, the greater the therapeutic affect. However, those of ordinary skill in the art would understand the correct dosage to be given to a particular subject, based on experience and the seriousness of the condition.

[**0072**] The daily dosages of extracts of *Artemisia spp*. and CB1 antagonist can be administered together in from 1 to 10 dosages, with the preferred number of dosages from 1 to 4 times a day, most preferably 1 to 2 times a day. The administration is preferably oral administration, although other forms of administration that provides a unit dosage of extracts of *Artemisia spp*. and CB1 antagonist may be used.

[**0073**] When used in accordance with the methods of the present invention, the extracts of *Artemisia spp*. may be administered in an amount more than, equal to or less than the conventional full-strength dose as a single-administered product. For example, the extracts of *Artemisia spp*. may be administered in an amount of from 10-100%, preferably about 25-100%, most preferably about 50-80%, of the conventional full-strength dose as a single-administered product.

C. CB1 Antagonists

[**0074**] The inventive compositions of the present invention include a CB1 antagonist and a dyslipidemic agent and/or a metabolic regulator. CB1 is one of the two known receptors in the endocannabinoid (EC) system, and has been associated with food intake. Blocking the CB1 receptor may reduce cravings for food, and may offer a promising approach to treating obesity. CB1 receptor blockade improves risk factors such as insulin resistance and dyslipidemia, both directly and indirectly through a reduction in intra-abdominal adipose tissue. Preferred CB1 blockers/antagonists/ inhibitors in accordance with the present invention include rimonabant (under development by Sanofi-Aventis), and other molecules capable of antagonizing the CB1 receptor that are currently under development or which may be discovered in the future.

[**0075**] The present invention may incorporate now known or future known CB1 antagonists in an amount generally recognized as safe. Generally, the effect of the CB1 antagonist is dose dependent, *i.e.*, the higher the dose, the greater the therapeutic affect. However, the effect of each CB1 antagonist is different, and therefore the level of therapeutic effect of a CB1 antagonist cannot be necessarily be directly correlated to the level of therapeutic effects of other CB1 antagonists. However, those of ordinary skill in the art would understand the correct dosage to be given to a particular subject, based on experience and the seriousness of the condition.

[**0076**] The daily dosages of CB1 antagonist and dyslipidemic agent and/or metabolic regulator can be administered together in from 1 to 10 dosages, with the preferred number of dosages from 1 to 4 times a day, most preferably 1 to 2 times a day. The administration is preferably oral administration, although other forms of administration that provides a unit dosage of CB1 antagonist and dyslipidemic agent and/or metabolic regulator may be used.

[**0077**] When used in accordance with the methods of the present invention, the CB1 antagonist may be administered in an amount more than, equal to or less than the conventional full-strength dose as a single-administered product. For example, the CB1 antagonist may be administered in an amount of from 10-100%, preferably about 25-100%, most preferably about 50-80%, of the conventional full-strength dose as a single-administered product.

D. Optional Additional Ingredients

[**0078**] The active ingredients of the present invention may optionally be co-administered with one or more additional compounds, or provided in a unit dose pharmaceutical formulation with one or more additional compounds, where those additional compounds are useful in improving lipid profiles, or are effective in treating any of the various conditions that are often associated with dyslipidemia. These associated conditions may include obesity, type II diabetes, hypertension, and/or metabolic syndrome.

[**0079**] These additional compounds may be selected from the group consisting of other compounds used in the treatment of obesity, type II diabetes and/or metabolic syndrome, and high blood pressure, and mixtures thereof, including those so commonly used. Anti-obesity agents may include melanocortin receptor (MC4R) agonists, melanin-concentrating hormone receptor (MCHR) antagonists, growth hormone secretagogue receptor (GHSR) antagonists, orexin receptor antagonists, CCK (cholecystokinin) agonists, GLP-1 agonists, NPY1 or NPY5 antagonists, corticotropin releasing factor (CRF) antagonists, histamine receptor-3 (H3) modulators, beta-3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, serotonin receptor agonists, aP2 inhibitors, thyroid receptor agonists and anorectic agents. Anti-diabetic agents/agents for treating metabolic syndrome may include antihyperglycemic agents including insulin secretagogues or insulin sensitizers, biguanides, sulfonyl ureas, glucosidase inhibitors, aP2 inhibitors, SGLT2 inhibitors, glycogen phosphorylase inhibitors, glucagon-like peptide-1 (GLP-1), PTP-1B (protein

tyrosine phosphatase-1B) inhibitors, 11β-HSD 1 (11β-hydroxy-steroid dehydrogenase 1) inhibitors and/or meglitinides, as well as insulin. Anti-hypertensive agents may include ACE inhibitors, angiotensin II receptor antagonists, NEP/ACE inhibitors, as well as calcium channel blockers, β-adrenergic blockers, and diuretics.

[**0080**] The additional compounds in accordance with the present invention may also be selected from dihydropyridine calcium channel blockers (preferably including, but not limited to, Bay K 8644, amlodipine (e.g., Norvasc®), felodipine (e.g., Plendil®), lacidipine (e.g., Lacipil®), lercanidipine (e.g., Zanidip®), nicardipine (e.g., Cardene®), nifedipine (e.g., Adalat®, Procardia®), nimodipine (e.g., Nimotop®), nisoldipine (e.g., Sular®), nitrendipine and isradipine (e.g., DynaCirc®)); antiarrhythmic agents (preferably including, but not limited to, quinidine, procainamide, disopyramide, lidocaine, mexiletine, tocainide, phenytoin, encainide, flecainide, moricizine, propafenone, esmolol, propranolol, acebutolol, metoprolol, amiodarone, azimilide, bretylium, clofilium, dofetilide, ibutilide, sematilide, sotalol, verapamil, mebefradfil, diltiazem adenosine, and digoxin); bile acid sequestrants (preferably including, but not limited to, cholestyramine, cholestipol, and colesevelam); antiplatelet drugs (including, but not limited to, aspirin, clopidogrel, ticlopidine, dipyridamole, abeiximab, tirofiban, eptifibatide, anagrelide, and ifetroban); and pharmaceutically acceptable esters, derivatives, conjugates, precursors or salts thereof, and mixtures thereof.

[**0081**] Also envisioned in accordance with the present invention is the use of similar compounds to those set forth above, which may be discovered in the future, or already existing compounds that may be approved for new uses in the future.

[**0082**] The optional additional ingredients, when provided, are included in amounts that are sufficient to regulate lipid levels, and/or treat a related condition that aggravates or is aggravated by dyslipidemia. The optional additional ingredients are provided in amounts that are generally regarded as safe and effective. Such amounts may include those amounts that are in accordance with prescribing information available for the

ingredients, as well as amounts that are higher or lower than the amounts described in prescribing information.

2. Administration of CB1 antagonist and Dyslipidemic Agent and/or Metabolic Regulator

[0083] The present invention also relates to the administration of a CB1 antagonist and a dyslipidemic agent and/or a metabolic regulator, optionally including another dyslipidemic agent, or any of the other optional compounds described above that are considered useful for treating dyslipidemia, obesity, hypertension, type II diabetes, metabolic syndrome, or any of the various other conditions often associated therewith. The dyslipidemic agent and/or metabolic regulator may be administered simultaneously with administration of the CB1 antagonist, *e.g.*, as a single fixed dosage pharmaceutical composition or as separate compositions administered at the same time.

[0084] In other preferred embodiments, the administration comprises a dyslipidemic agent and/or a metabolic regulator and a CB1 antagonist, wherein the dyslipidemic agent and/or metabolic regulator is administered apart from the administration of the CB1 antagonist, but in a concomitant treatment regime. For example, the CB1 antagonist may be administered once-a-day, with multiple daily administrations of the dyslipidemic agent and/or metabolic regulator. One skilled in the art with the benefit of the present disclosure will understand that the precise dosage and schedule for the administration of the dyslipidemic agent and/or metabolic regulator and the CB1 antagonist will vary depending on numerous factors, such as, for example, the route of administration and the seriousness of the condition. For example, the dyslipidemic agent and/or metabolic regulator and one or more CB1 antagonists may be administered in accordance with the amounts and dosing regimens described herein above.

3. Dosage Forms

[**0085**] The composition comprising a CB1 antagonist and a dyslipidemic agent and/or a metabolic regulator may be prepared in the form of a capsule, such as a hard gelatin capsule, a tablet, a powder that can be dispersed in a beverage, a liquid, or a soft gel capsule. The composition may also be contained in a liquid suitable for injection or infusion. Such dosage forms may be prepared using techniques that are known to those skilled in the art, and may include, for example, those set forth in Remington's Pharmaceutical Sciences (now re-titled Remington's: the Science and Practice of Pharmacy). However, the methods of preparing the inventive compositions for administration are not to be limited to any particular dosage form. Rather, they may be prepared as any pharmaceutically acceptable dosage form, including other solid oral dosage forms, other liquid oral dosage forms, and any other suitable dosage forms. When provided, the one or more optional additional ingredients may also be provided in the dosage form, so as to create a convenient unit dose form.

[**0086**] In some embodiments, the unit dose formulations of the present invention may allow for improved effectiveness of each active ingredient, with one or both administered as a conventional full-strength dose, as compared to the formulations in the prior art. In other embodiments, the formulations of the present invention may allow for reduced dosages of the optional additional ingredients, as compared to the formulations in the prior art, while still maintaining or even improving upon the effectiveness of each active ingredient.

[**0087**] The active ingredients of the present invention may be administered with a combination of one or more non-active pharmaceutical ingredients (also known generally herein as "excipients"). Non-active ingredients, for example, serve to solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, protect, color, flavor, and/or fashion the active ingredients into an applicable and efficacious preparation that is safe, convenient, and otherwise acceptable for use. Such non-active pharmaceutical ingredients are known to those skilled in the art, and may include, for example, those

set forth in Remington's Pharmaceutical Sciences (now re-titled Remington's: the Science and Practice of Pharmacy).

[**0088**] Excipients include surfactants, such as propylene glycol monocaprylate, mixtures of glycerol and polyethylene glycol esters of long fatty acids, polyethoxylated castor oils, glycerol esters, oleoyl macrogol glycerides, propylene glycol monolaurate, propylene glycol dicaprylate/dicaprate, polyethylene-polypropylene glycol copolymer, and polyoxyethylene sorbitan monooleate, cosolvents such ethanol, glycerol, polyethylene glycol, and propylene glycol, and oils such as coconut, olive or safflower oils. The use of surfactants, cosolvents, oils or combinations thereof is generally known in the pharmaceutical arts, and as would be understood to one skilled in the art, any suitable surfactant may be used in conjunction with the present invention and embodiments thereof.

[**0089**] The present combinations of a CB1 antagonist and a dyslipidemic agent and/or a metabolic regulator, optionally including one or more additional ingredients, taken from the list set forth above, may allow for a greater effect than any expected combined or additive effect of the compounds alone. Thus, the combined treatment using the active ingredients, separately or through the novel combination product of the present invention, may cause an unexpected increase in effect of the active ingredients. This may allow increased effectiveness with standard dosages, or, alternatively, may allow maintained effectiveness with reduced dosages of the active ingredients. It is well accepted in practice that an improved bioavailability or effectiveness of a drug or other active ingredient allows for an appropriate reduction in the daily dosage amount. Any undesirable side effects may also be reduced as a result of the lower dosage amount and the reduction in use of excipients (*e.g.*, surfactants).

4. Alternative Embodiments

[**0090**] Additional uses for the compositions and methods of the present invention, beyond treating various dyslipidemias, including hypertriglyceridemia,

hypercholesteremia, and mixed dyslipidemia; treating vascular disease; treating artherosclerotic disease; treating or preventing conditions characterized by the presence of dyslipidemias, vascular disease, and/or atherosclerotic disease; treating obesity; preventing or reducing cardiovascular and vascular events; reducing insulin resistance, fasting glucose levels and postprandial glucose levels; treating and/or preventing diabetes and/or symptoms thereof; and reducing the incidence of and/or delaying the onset of type II diabetes and/or metabolic syndrome, are also envisioned. The compositions may also be beneficially incorporated into preparations for use in the treatment of these and other conditions.

[**0091**] It will, of course, be appreciated that the above description has been given by way of example only and that modifications in detail may be made within the scope of the present invention.

[**0092**] Throughout this application, various patents and publications have been cited. The disclosures of these patents and publications in their entireties are hereby incorporated by reference into this application, for example, in order to more fully describe the state of the art to which this invention pertains.

[**0093**] The invention is capable of considerable modification, alteration, and equivalents in form and function, as will occur to those ordinarily skilled in the pertinent arts having the benefit of this disclosure.

[**0094**] While the present invention has been described for what are presently considered the preferred embodiments, the invention is not so limited. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the detailed description provided above.

What is Claimed:

1. A pharmaceutical formulation comprising at least one dyslipidemic agent selected from the group consisting of DPP4 inhibitors, MTP inhibitors, PPAR agonists/antagonists, and omega-3 fatty acids, and at least one compound that acts as an antagonist of CB1 receptors.

2. The pharmaceutical formulation of claim 1, wherein the formulation further comprises at least one metabolic regulator selected from the group consisting of sarsasapogenin, smilagenin, steroidal glycosides and extracts thereof, and extracts of *Artemisia spp*.

3. The pharmaceutical formulation of claim 1, wherein the formulation further comprises at least one additional compound useful for treating hypertriglyceridemia, hypercholesteremia, mixed dyslipidemia, vascular disease, artherosclerotic disease, and/or obesity; preventing and/or reducing cardiovascular and/or vascular events; and reducing insulin resistance, fasting glucose levels and/or postprandial glucose levels.

4. The pharmaceutical formulation of claim 1, wherein the formulation further comprises at least one additional compound useful for preventing, reducing the incidence of, and/or delaying the onset of type II diabetes.

5. The pharmaceutical formulation of claim 3, wherein the at least one additional compound is selected from the group consisting of CAIs, statins, CETP inhibitors, niacin derivatives, and LXR agonists/antagonists.

6. The pharmaceutical formulation of claim 3, wherein the at least one additional compound is at least one anti-obesity agent, selected from the group consisting of melanocortin receptor (MC4R) agonists, melanin-concentrating hormone receptor (MCHR) antagonists, growth hormone secretagogue receptor (GHSR) antagonists,

orexin receptor antagonists, CCK (cholecystokinin) agonists, GLP-1 agonists, NPY1 antagonists, NPY5 antagonists, corticotropin releasing factor (CRF) antagonists, histamine receptor-3 (H3) modulators, beta-3 adrenergic agonists, lipase inhibitors, serotonin reuptake inhibitors, dopamine reuptake inhibitors, serotonin receptor agonists, aP2 inhibitors, thyroid receptor agonists, and anorectic agents.

7. The pharmaceutical formulation of claim 4, wherein the at least one additional compound is at least one anti-diabetic agent, selected from the group consisting of antihyperglycemic agents, insulin secretagogues, insulin sensitizers, biguanides, sulfonyl ureas, glucosidase inhibitors, aP2 inhibitors, SGLT2 inhibitors, glycogen phosphorylase inhibitors, glucagon-like peptide-1 (GLP-1), PTP-1B (protein tyrosine phosphatase-1B) inhibitors, 11β-HSD 1 (11β-hydroxy-steroid dehydrogenase 1) inhibitors, meglitinides, and insulin.

8. The pharmaceutical formulation of claim 3, wherein the at least one additional compound is at least one anti-hypertensive agent, selected from the group consisting of ACE inhibitors, angiotensin II receptor antagonists, NEP/ACE inhibitors, calcium channel blockers, β-adrenergic blockers, and diuretics.

9. The pharmaceutical formulation of any one of claims 1-8, wherein the formulation is provided as a unit dosage.

10. A pharmaceutical formulation comprising at least one metabolic regulator selected from the group consisting of sarsasapogenin, smilagenin, steroidal glycosides and extracts thereof, and extracts of *Artemisia spp.*, and at least one compound that acts as an antagonist of CB1 receptors.

11. The pharmaceutical formulation of claim 10, wherein the formulation further comprises at least one dyslipidemic agent selected from the group consisting of DPP4 inhibitors, MTP inhibitors, PPAR agonists/antagonists, and omega-3 fatty acids.

12. The pharmaceutical formulation of claim 10, wherein the formulation further comprises at least one additional compound useful for treating hypertriglyceridemia, hypercholesteremia, mixed dyslipidemia, vascular disease, artherosclerotic disease, and/or obesity; preventing and/or reducing cardiovascular and/or vascular events, and reducing insulin resistance, fasting glucose levels and/or postprandial glucose levels.

13. The pharmaceutical formulation of claim 10, wherein the formulation further comprises at least one additional compound useful for preventing, reducing the incidence of, and/or delaying the onset of type II diabetes.

14. The pharmaceutical formulation of claim 12, wherein the at least one additional compound is selected from the group consisting of CAIs, statins, CETP inhibitors, niacin derivatives, and LXR agonists/antagonists.

15. The pharmaceutical formulation of claim 12, wherein the at least one additional compound is at least one anti-obesity agent, selected from the group consisting of melanocortin receptor (MC4R) agonists, melanin-concentrating hormone receptor (MCHR) antagonists, growth hormone secretagogue receptor (GHSR) antagonists, orexin receptor antagonists, CCK (cholecystokinin) agonists, GLP-1 agonists, NPY1 antagonists, NPY5 antagonists, corticotropin releasing factor (CRF) antagonists, histamine receptor-3 (H3) modulators, beta-3 adrenergic agonists, lipase inhibitors, serotonin reuptake inhibitors, dopamine reuptake inhibitors, serotonin receptor agonists, aP2 inhibitors, thyroid receptor agonists, and anorectic agents.

16. The pharmaceutical formulation of claim 13, wherein the at least one additional compound is at least one anti-diabetic agent, selected from the group consisting of antihyperglycemic agents, insulin secretagogues, insulin sensitizers, biguanides, sulfonyl ureas, glucosidase inhibitors, aP2 inhibitors, SGLT2 inhibitors, glycogen phosphorylase inhibitors, glucagon-like peptide-1 (GLP-1), PTP-1B (protein tyrosine

phosphatase-1B) inhibitors, 11β-HSD 1 (11β-hydroxy-steroid dehydrogenase 1) inhibitors, meglitinides, and insulin.

17. The pharmaceutical formulation of claim 12, wherein the at least one additional compound is at least one anti-hypertensive agent, selected from the group consisting of ACE inhibitors, angiotensin II receptor antagonists, NEP/ACE inhibitors, calcium channel blockers, β-adrenergic blockers, and diuretics.

18. The pharmaceutical formulation of any one of claims 10-17, wherein the formulation is provided as a unit dosage.

19. A pharmaceutical formulation comprising omega-3 fatty acids and at least one CB1 receptor antagonist.

20. The pharmaceutical formulation of claim 19, wherein the omega-3 fatty acids are present in a concentration of at least 40% by weight as compared to the total fatty acid content of the composition.

21. The pharmaceutical formulation of claim 19, wherein the omega-3 fatty acids are present in a concentration of at least 80% by weight as compared to the total fatty acid content of the composition.

22. The pharmaceutical formulation of claim 19, wherein the omega-3 fatty acids comprise at least 50% by weight of EPA and DHA as compared to the total fatty acid content of the composition.

23. The pharmaceutical formulation of claim 19, wherein the omega-3 fatty acids comprise at least 80% by weight of EPA and DHA as compared to the total fatty acid content of the composition.

24. The pharmaceutical formulation of claim 19, wherein the omega-3 fatty acids comprise about 5% to about 95% by weight of EPA as compared to the total fatty acid content of the composition.

25. The pharmaceutical formulation of claim 19, wherein the omega-3 fatty acids comprise about 40% to about 55% by weight of EPA as compared to the total fatty acid content of the composition.

26. The pharmaceutical formulation of claim 19, wherein the omega-3 fatty acids comprise about 5% to about 95% by weight of DHA as compared to the total fatty acid content of the composition.

27. The pharmaceutical formulation of claim 19 or 25, wherein the omega-3 fatty acids comprise about 30% to about 60% by weight of DHA as compared to the total fatty acid content of the composition.

28. The pharmaceutical formulation of claim 19, wherein omega-3 fatty acids comprise omega-3 polyunsaturated fatty acids, esters of omega-3 fatty acids with glycerol, esters of omega-3 fatty acids and a primary, secondary or tertiary alcohol, or mixtures thereof.

29. The pharmaceutical formulation of claim 19, wherein the omega-3 fatty acids comprise EPA and DHA in a ratio of EPA:DHA from 99:1 to 1:99.

30. The pharmaceutical formulation of claim 19, wherein the omega-3 fatty acids comprise EPA and DHA in a ratio of EPA:DHA from 2:1 to 1:2.

31. A pharmaceutical formulation comprising a PPAR agonist/antagonist and at least one CB1 receptor antagonist.

32. The pharmaceutical formulation of claim 31, wherein the PPAR agonist and/or antagonist is selected from the group consisting of PPAR-alpha modulators, PPAR-delta modulators, PPAR-gamma modulators, and dual-PPAR modulators.

33. The pharmaceutical formulation of claim 31, wherein the PPAR agonist and/or antagonist comprises a fibrate.

34. The pharmaceutical formulation of claim 31, wherein the PPAR agonist and/or antagonist comprises fenofibrate.

35. A method of administering the pharmaceutical formulations of any one of claims 1-34, wherein said method comprises providing the formulation to a patient in need thereof.

36. A method of administering the pharmaceutical formulations of any one of claims 1-34, wherein said method comprises providing the formulation to a patient in need thereof as a unit dosage product.

37. A method of treating a patient suffering from at least one condition independently selected from the group consisting of hypertriglyceridemia, hypercholesteremia, mixed dyslipidemia, vascular disease, artherosclerotic disease and related conditions, diabetes and/or symptoms thereof, and obesity, comprising administering to a patient suffering therefrom the pharmaceutical formulation of any one of claims 1-34.

38. A method of preventing and/or reducing cardiovascular and/or vascular events, comprising administering to a patient at risk for experiencing cardiovascular and/or vascular events the pharmaceutical formulation of any one of claims 1-34.

39. A method of reducing insulin resistance, fasting glucose levels and/or postprandial glucose levels comprising administering to a patient suffering from

metabolic syndrome and/or type II diabetes the pharmaceutical formulations of any one of claims 1-34.

40. A method of preventing, reducing the incidence of, and/or delaying the onset of type II diabetes comprising administering to a patient at risk for developing type II diabetes the pharmaceutical formulations of any one of claims 1-34.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/03728

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/00; A01N 43/78 (2008.04)
USPC - 514/213.01; 514/369
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A01N 43/00; A01N 43/78 (2008.04)
USPC - 514/213.01; 514/369

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A01N 37/00, 37/02, 37/06, 37/10; A61K 31/55, 31/19, 31/425, 31/20, 31/225 (2008.04)
USPC - 514/571, 560, 547

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT,PGPB,EPAB,JPAB); Google
Search Terms Used:
DPP4 inhibitor, omega-3 fatty acid, CB-1 receptor antagonist, eicosapentaenoic, sarsasapogenin, smilagenin, diabetes

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 2006/0160850 A1 (SUN et al.) 20 July 2006 (20.07.2006), para [0158-0202]	1-18 and 31-34 ----- 19-30
Y	US 6,284,268 B1 (MISHRA et al.) 04 September 2001 (04.09.2001), col 1, 6, 9 and 20	19-30

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 June 2008 (11.06.2008)	19 JUN 2008

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/03728

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 35-40
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.